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| 10/518,610 | 06/16/2005 | Ghanem Elias Ghanem | 27656/40760 | 3634 |

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| EXAMINER | |
|---|---|
| GUPTA, ANISH | |

| ART UNIT | PAPER NUMBER |
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| 1654 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/518,610 | GHANEM ET AL. | |
| | Examiner | Art Unit | |
| | ANISH GUPTA | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,6,7,11,16,18 and 20-24* is/are pending in the application.

4a) Of the above claim(s) *23 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,7,11,16,18 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-3-09 has been entered.

2. Newly submitted claims 23-24 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The newly added claims are drawn to method of treating cancer and method of treating other disorders selected from AIDs, parasitic disease etc. . . These claims corresponded to Group III in the restriction requirement mailed 10-4-07. In response to the restriction requirement, Applicants canceled all of the claims drawn to Groups II-VI. Examination was conducted on the claims corresponding to Group I.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 23-24 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. All rejections made in the previous office action and not cited herein are hereby withdrawn.

### New Grounds For Rejections

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-2, 6, 11, 16, 18- 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 is extremely confusing. The claim states that the drug being connected to said tripeptide via its not terminal proteolytic enzyme cleavable amino acids moiety. It is unclear how the drug is connected to the tripeptide since a the claim utilizes a negative when describing the connection. Thus, it is unclear if "not terminal" describes the conjugation of the drug to the peptide, meaning that the peptide cannot be conjugated to the drug via its terminal amino acid moiety or just the terminal end of the amino acid. Taken differently, it is unclear if "not terminal" just describes the amino acid in the tripeptide. That is, for example, proline in the tripeptide Phe-Phe-Pro is not a proteolytic enzyme cleavable amino acid moiety.

Clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-2, 6, 11, 16, 18- 20, 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

**New Matter**

Note that this rejection is made when claim 1 is interpreted to mean that that the conjugation of the drug is not through the terminal proteolytic enzyme cleavable amino acid moiety.

Claim 1 is drawn to a tripeptide or tripeptide ester which is connected to a drug, "said drug being connected to said tripeptide via its not terminal proteolytic enzyme cleavable amino acid moiety." This limitation, when interpreted, as a linkage of the drug not occurring through the terminal proteolytic enzyme cleavable amino acid moiety constitutes new matter.

Claim 21 states that the peptide is "substituted or unsubstituted." However, base claim 7 requires that the "tripeptide comprise a substitution at the not terminal amino acid moiety." Thus, the claim lacks antecedent basis for the limitation "unsubstituted."

**Lack of literal support**

The specification does not provide any literal support that the linkage of the drug cannot occur through the terminal proteolytic enzyme cleavable amino acid moiety. The specification, on page 4, generally describes the linkage between the drug and the peptide. However, the specification does not set for a negative limitation that the linkage cannot occur through the terminal proteolytic enzyme cleavable amino acid moiety.

**Lack of Inherent support**

While there is no in haec verba requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure. Thus, the specification can provide implicit or inherent support. However, the specification fails to provide any inherent support for the claimed limitation. In fact the specification describes the opposite. On page 3, the specification states "if the transport and delivery system is drug loaded, then the cleavable amino acid, in particular the pharmacologically active group or site substituted phenylalanine moiety, can not only be substituted by the drug but be the drug." This page would imply that the terminal amino acid can be utilized in the linkage with the drug. The specification states that terminal amino acid is modified so that the it can be coupled to the drug (see page 5). Thus, the specification does not provide any implicit support that said drug being connected is not connected through the terminal proteolytic enzyme cleavable amino acid moiety.

**Written Description**

6. Claims 7-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.
The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107

> F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP states that for a genus claim, written

description may be satisfied by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.. Further, the MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims recite a tripeptide comprising a proteyolytic enzyme cleavable amino acid moiety and the tripeptide comprising a substituent at the not terminal amion acid moiety, said subsitutent being sufficiently reactive to be useful in drug coupling reaction and said substituent is not -N(CH2-CH2-Cl)2. This generic statement for the substituent on the tripeptide does not provide ample written description for the compounds since the claims do not define the requisite relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics. The substituent is solely defined by its function in that it is reactive and can be used in drug coupling reactions. The specification does not provide ample structural insight into this substituent, aside from the proviso that it is not -N(CH2-CH2-Cl)2.

As stated earlier, the MPEP states that written description for a genus can also achieved by a representative number of species within a broad generic. It is unquestionable claim 7 is a broad generic with respect all possible modified peptides that can be defined for the claim. While the claim may define the specific tripeptide, this is of little help with respect to the reactive substitution on the not terminal amino acid moiety. The possible structural variations are limitless to any reactive substation. The claim, when interpreted broadly, can read upon modified peptides that have significant changes in the side chain of the amino acids. Furthermore, the specification does not provide a single disclosure of a likely substituent that can be utilized. The specification only describes the substituent in generic terminology, i.e. being sufficiently reactive to be useful in drug coupling reaction. The examples in the specification only utilize the substituent that has been specifically provisioned out of the claims. The specification simply fails to provide for any other modified peptides that have a reactive moiety on not terminal amino acid. Given the specification, one cannot readily conclude that applicant was in possession of the broad genus of the tripeptide with any reactive modification at the not terminal amino acid. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

***Claim Rejections - 35 USC § 102***

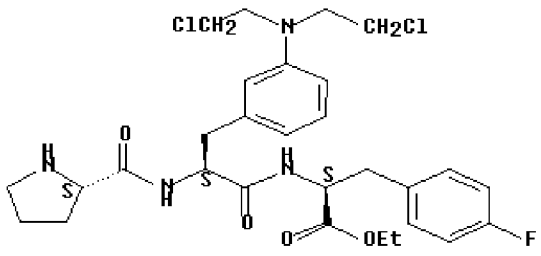
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-2, 6, 16, 18 and 20 are rejected under 35 U.S.C. 102(b) as being anticipate by Barbieri (US3814746).

The claims are drawn to tripeptide linked to a therapeutic drug.

The US patent claims a compound of tetracycline linked to a peptide (see col. 1). The US patent specifically claims and discloses a tetracycline linked to the peptide Ser-p-F-Phe-(m-di(2-chloroethyl)-Phe (see col. 3 and claim 1). Note that the core peptide taught is Ser-Phe-Phe, which is one of the peptides claimed. While the peptide has a substitution, the claims do allow for substitution within the side chains. The reference also teaches the linkage of the tetracycline with the sequence of the formula:



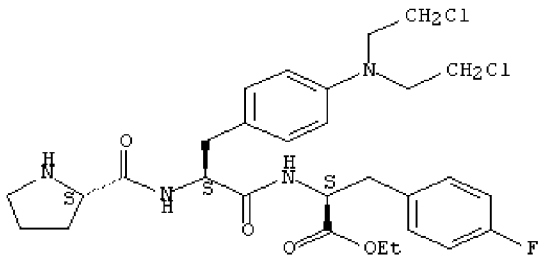

The conjugation to the tetracycline residue occurs through the prolyl residue, which not the proteolytic enzyme cleavable amino acid moiety (see col. 1, lines 40-61 and col. 2, lines 15-30). Note that this sequence is Pro-Phe-f-Phe.

Thus, the prior art meets the limitation of the claim.

8. Claims 7, 21-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Lewensohn et al. (WO01/96367).

The claims are drawn to a tripeptide or tripeptide esters selected, where the tripeptide includes Pro-Phe-Phe and has a substituent at the not terminal amino acid moiety, with the proviso that said substituent is not ---N(CH2-CH2-Cl)2 in the meta position on the not terminal Pro-Phe-p-F-Phe.

The reference disclose the compound:




.

This compound is L-prolin-L-melphanyl-p-Fluorophenylalaline etlyl ester (see claims). Note that the peptide sequence is Pro-phe-F-Phe, which meets the limitation of claims 21-22. While the compound contains the substituent N(CH2-CH2-Cl)2 in the not terminal Phe residue, it does meet the limitation of the claim since the substitution is in the para position and not meta.

Thus, the reference anticipates the claims.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (571)272-0965. If attempts to reach

the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can normally be reached on (571) 272-0562. The fax phone number of this group is (571)-273-8300.

/Anish Gupta/
Primary Examiner, Art Unit 1654